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14. ABSTRACT
The purpose of this study is to investigate mechanisms of disequilibrium and imbalance in veterans of Operation Enduring Freedom / Operation Iraqi Freedom who have experienced traumatic brain injury (TBI). The mechanism of chronic dizziness and imbalance after TBI is not known. The hypothesis for this study is that TBI leads to an impairment in the vestibular reflexes that compensate for linear movements of the head and body during standing and walking. The experimental protocol has two parts. First, we use an infrared motion-tracking system to record the movements of the body during balance and walking tasks. Then, we use eye movement recordings during linear and rotational motion to perform a comprehensive assessment of the vestibular reflexes. Data recorded in veterans with a history of TBI are compared to those from neurologically normal control subjects who report no balance problems. To date, we have studied six veterans with TBI and five control subjects, and recruitment is ongoing. Preliminary data have confirmed objective balance and gait data in TBI subjects, but it is not yet clear whether these abnormalities will correlate with specific vestibular deficits.

15. SUBJECT TERMS
Traumatic brain injury, balance, locomotion, vestibular, eye movements

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INTRODUCTION

The objective of this study is to investigate mechanisms of balance impairment in veterans of Operation Enduring Freedom / Operation Iraqi Freedom (OEF/OIF) who have experienced traumatic brain injury (TBI). Persistent disequilibrium is a known post-concussive symptom, and recent surveys of veterans have confirmed that this is also true of blast-related mild TBI (Cave et al. 2007; Scherer et al. 2007; Scherer and Schubert 2009). Prior studies in civilians have documented objective impairments in balance and locomotion after TBI, but studies have not been conducted following combat-related TBI, and it is not known whether blast injuries produce balance deficits that are similar to those that occur after blunt TBI in civilians. Moreover, in neither group has the relationship of these deficits to vestibular injury been adequately explored. Specifically, little is known about the effect of blast-exposure and TBI on the reflexes derived from the otolith organs of the vestibular labyrinth (the organs that respond to linear motion and sense gravitational acceleration). These reflexes are likely to be of particular importance for balance and equilibrium. The hypothesis of this study is that impaired otolith reflexes account for persistent dizziness and gait impairment after traumatic brain injury. We are testing this hypothesis in a series of experiments designed to measure directly the otolith- and canal-mediated vestibulo-ocular reflexes and to correlate these to quantitative measures of static and dynamic balance and of walking. The results of this study will not only provide critical information regarding the pathophysiologic mechanisms of balance impairment after TBI, but they will also facilitate improved diagnosis of these problems in the acute and chronic settings.

Our effort in the second year of this study has been focused on continued recruitment and testing of veterans with a history of TBI and normal subjects, on developing software tools to analyze both gait and balance data, and eye movement recordings from our vestibular tests. Our consultant statisticians are working closely with us to model the data and choose appropriate and valid statistical measures to assess results, in particular with regard to gait and balance tests, given the high complexity and large number of degrees-of-freedom of these data.

BODY

TASK 1: VOR Measurements

This task addresses Specific Aim 1: Are vestibulo-ocular reflexes impaired in TBI subjects with disequilibrium? To test this hypothesis, we compare eye movements during translational head motion (the translational vestibulo-ocular reflex, TVOR) between control and TBI subjects. Measurements are performed on our Moog motion platform using scleral coils to record eye movements. Responses to horizontal and vertical linear translations and to horizontal rotations are recorded. Our hypothesis predicts a specific deficit in translational vestibular responses, i.e. eye movements evoked by stimulation of the otolith organs.

So far, we have recorded data from six subjects with TBI and five normal subjects, although we have data from a much larger group of normal subjects from prior studies. Unlike gait and balance measures (see below), the TVOR findings have been less consistent so far in support of our hypothesis. Figure 1 (Appendix) shows the TVOR gains (ratio of eye velocity to ideal eye velocity) for 2 Hz translation (horizontal and vertical gains averaged). Consistent with our prior studies (Liao et al. 2008), there is a wide range of TVOR gains in the normal subjects. This is different from the rotational VOR and makes it potentially more difficult to assess differences between the groups. TVOR gains from the TBI group overlap those of the control subjects considerably, but there are nonetheless two TBI subjects who have gains that are lower than those of normal subjects, even previously studied subjects, some of whom were much older than these veterans (Liao et al. 2008). The difference in the gains of these two subjects from the control group is even more clear when considering the initial, rather than steady state responses (Figure 1, right panel). Responses closer to motion onset are more likely to reflect the primary vestibular response.

There are several possible explanations for our failure to find TVOR gain abnormalities in more TBI subjects, even though gait and balance deficits (see Task 2 below) are common in this group. First, it may be that the TVOR gain is not a sufficiently sensitive measure for the degree of impairment that these individuals have. Although we are attempting to study TBI veterans over a range of injury and balance severities, most of our subjects so far have had only mild balance impairment from a functional standpoint. Second, it may be that vestibulo-ocular reflexes are not affected in the same way as the vestibulo-spinal reflexes that control balance. Third, it is possible that balance deficits are multifactorial after TBI, consisting of a combination of vestibular dysfunction and other motor control abnormalities, and that the relative contribution of these components may differ among individuals. Finally, since we are often unable to study veterans near to the time of injury, it may be that partial recovery and adaptation processes that have already occurred are obscuring the extent of a vestibular injury in some cases.

Regardless of the variability of the group responses, it remains of great interest that two veterans appear to have low TVOR gains. This at least suggests that vestibular impairment may be an important contributor to imbalance in some, if not all, TBI cases.

TASK 2: Gait and Balance Measurements

This task is performed in tandem with Task 1. Each subject in whom we record vestibular responses also undergoes testing of gait and balance function. In the past year, we have acquired sufficient data from control and TBI subjects, and we have completed enough preliminary data analysis to confirm clear differences in equilibrium and locomotion in TBI subjects, even in those with relatively mild TBI

and qualitatively normal neurological function. Here we will present data first regarding static balance (standing on foam with eyes open and closed) and then data from walking on foam. The key findings thus far are: 1) a decreased stability during quiet standing, especially with eyes closed, when vestibular input is particularly important, because visual cues cannot be used to determine one's orientation and stabilize posture, and 2) a gait impairment that includes both a decreased forward speed of walking and more lateral sway (decreased postural stability). There also appears to be an impairment of dynamic postural stability, as tested by sudden and temporally unpredictable forward and lateral body pulls; these data have not been sufficiently analyzed to provide a quantitative summary result at this time.

Static Balance while Standing on Foam

In this task, subjects stand on a surface that consists of a compressible foam whose uncompressed thickness is approximately 4 inches. Infrared reflective markers are attached on the body surface or tight-fitting clothing at the level of the head, neck (C7), trunk (sacrum, anterolateral pelvis), and lower extremities (knee, tibia, ankle, heel, toe) to measure body and leg kinematics. Surface EMG recordings are also made of relevant postural muscles; those data are in earlier stages of analysis and will not be presented here.

Data from each subject while standing on foam with eyes open and closed are presented in Figures 1-4 (Appendix). These are two-dimensional plots in which instantaneous position of the sacral marker (best single marker of body center) along the front-back (fore-aft) direction is plotted against the lateral (right-left) position. TBI subjects (Figures 2,4) show a greater amount and range of sway from the center position than do normal subjects (Figures 1,3). This is particularly true for the eyes-closed condition. Individuals in both groups had more sway with eyes closed, as expected, but there were several TBI subjects whose trunk movements were substantially increased by removal of vision.

There are a number of inter-related measures that could be used to quantify body sway during standing, such as amount or range of deviation from upright, sway velocity, and sway frequency. It is not clear which of these will best capture TBI-related balance deficits, and different measures may relate to specific components of the postural control system. We are investigating several of these measures, but for our initial data analysis, we have chosen a simple and straightforward measure that will quantify the total amount of body sway during a fixed amount of time (same time for each subject). This combines both fore-aft and lateral sway into a single measure and is effectively the line length of each trace in the plots of Figures 1-4. Results are shown in the box plot of Figure 5 (Appendix). These data at least two trends:

1.Increased sway path length in TBI subjects compared to control subjects both with eyes open (SACR: median 143 mm vs. 338 mm, $p = 0.05$, Wilcoxon rank sum; C7: median 173 mm vs. 340 mm, $p=0.03$) and eyes closed (SACR: median 251 mm vs. 841 mm, $p = 0.05$; C7; 158 mm vs. 843 mm, $p=0.08$).

2.Increased sway with eyes closed relative to eyes open for TBI subjects, especially for the neck target (C7: median 340 mm vs. 843 mm, $p = 0.06$).

Thus, these preliminary data confirm that veterans with a history of TBI have less postural stability than control subjects.

Gait Speed and Stability: Walking on Foam

As for static balance data, there are a number of possible measures by which to quantify gait. These include lumped body measures such as overall gait speed or body sway, as well as measures that are

based on the kinematics of motion of individual body segments or of joint angles. Both absolute measures and their variance may be informative (e.g., stride length vs. stride-length variability). For our initial analysis we have focused primarily on the simple and global measures, such as walking speed and lateral sway, in order to determine if we are likely to find differences between the groups. At the same time, we have been investigating a broader range of parameters.

Consistent with the findings in the first two TBI subjects, presented in our last annual report, our current data continue to show that veterans in the TBI group walk more slowly than do control subjects (Figure 5, Appendix). The median gait speed for control subjects, while walking on the foam surface, was 1496 mm/s, while that of the TBI subjects was 1210 mm/s (19% lower, $p = 0.03$, Wilcoxon rank sum). There was also a trend toward greater lateral sway in the TBI subjects, as measured by the standard deviation of the sacral marker position along the direction orthogonal to the movement direction (21.5 mm vs. 28.2 mm, $p = 0.08$).

In summary, the additional data acquired this year continue to support the preliminary impressions that veterans with TBI who report chronic disequilibrium have consistent gait and balance impairments. These include, at least, slower and less stable walking, and reduced postural stability while standing, particularly with eyes closed and while standing on foam, a condition that is most likely to require robust and accurate vestibular reflexes.

TASK 3: VOR Adaptation / Motor Learning

We have not yet begun this task, as we are focusing on completion of the primary portion of the study (Tasks 1 and 2). We are beginning to set up the protocol for these experiments.

Challenges to the Project .

The main challenge to the work thus far has been subject recruitment. Although we see a large number of OEF/OIF veterans in our facility with a history of TBI, we have discovered that many are not interested in participating in our research studies. We have also had several subjects who initially expressed interest but then later changed their minds and decided not to enroll. Particularly difficult is to recruit TBI subjects who have no disequilibrium, for two reasons: first, because not having dizziness, they are less interested, and second, because it appears to be a relative minority of our veterans with a TBI history that report no dizziness or equilibrium issues at all. To address these issues, we have considered combining TBI subjects into a single group, recruiting subjects with a range of dizziness severity and analyzing them based on the degree of their subjective dizziness and objective findings. Despite the slower than anticipated pace of enrollment, we are continuing to recruit actively. For example, we have another TBI subject scheduled to be tested within the next several days. Our findings thus far are promising, and we remain strongly committed to completing the project. If necessary, we would appreciate the opportunity to apply for a one-year no-cost extension at the end of the scheduled project period.

Personnel Changes

Due to Dr. Liao's transition to other projects within our laboratory, we are in the process of adding a new member of the research staff, who will assume some of Dr. Liao's responsibilities for this project. Dr. Tao Pan (curriculum vitae in Appendix) is an experienced engineer who holds a Ph.D. in electrical engineering from Case Western Reserve University and has worked extensively, at the Cleveland Clinic

and elsewhere, in biomedical engineering and instrumentation. He has all of the hardware and software skills that are essential to this project. When final approval of his appointment has been obtained from the IRB, those documents will be forwarded to USAMRMC.

KEY RESEARCH ACCOMPLISHMENTS

We have not completed recruitment and testing of subjects. Thus, it is not possible to make definitive conclusions from our data. At this stage, the key accomplishments are:

•We have successfully recorded ocular responses to translational motion in veterans with TBI and with normal subjects. Although the data are not conclusive as yet, they do suggest that there may be a subgroup of veterans with TBI in whom injury to the vestibular system (central or peripheral) is a key component of their balance problem.

•In detailed analysis of our preliminary data, we have found consistent gait and balance deficits after TBI. These include reduced gait speed and decreased postural stability while standing and walking.

REPORTABLE OUTCOMES

Because we are still recruiting subjects to the study, reports of our findings have been limited to date. We do anticipate that within the next year we will have sufficient data to begin to report our findings.

CONCLUSION

This study will provide critical new information regarding the effect of TBI on vestibular function and the relationship of vestibular impairment to gait and balance problems. Our data to date confirm a range of balance and walking disturbances in veterans with TBI. This is particularly noteworthy, considering that this group of veterans is young and has undergone extensive physical training as a part of their military service and thus would be expected to have exquisite balance and locomotion. As predicted, the balance deficits are much greater in a more challenging task, such as standing or walking on foam, a condition in which a greater reliance on vestibular mechanisms is expected. Further data are required to assess the overall relationship between balance and the TVOR, but the fact that two of six TBI subjects have TVOR responses below the range of normal subjects is an important finding. The study will provide key information regarding the nature and mechanisms of combat-related traumatic injury. We anticipate that it will lead to improved diagnostic techniques for assessing functional impairment related to vestibular injury (which could be important for determining a veteran's capacity for performing duties that may depend on robust balance) and that it will help to improve and refine rehabilitative strategies for this important problem.

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APPENDIX

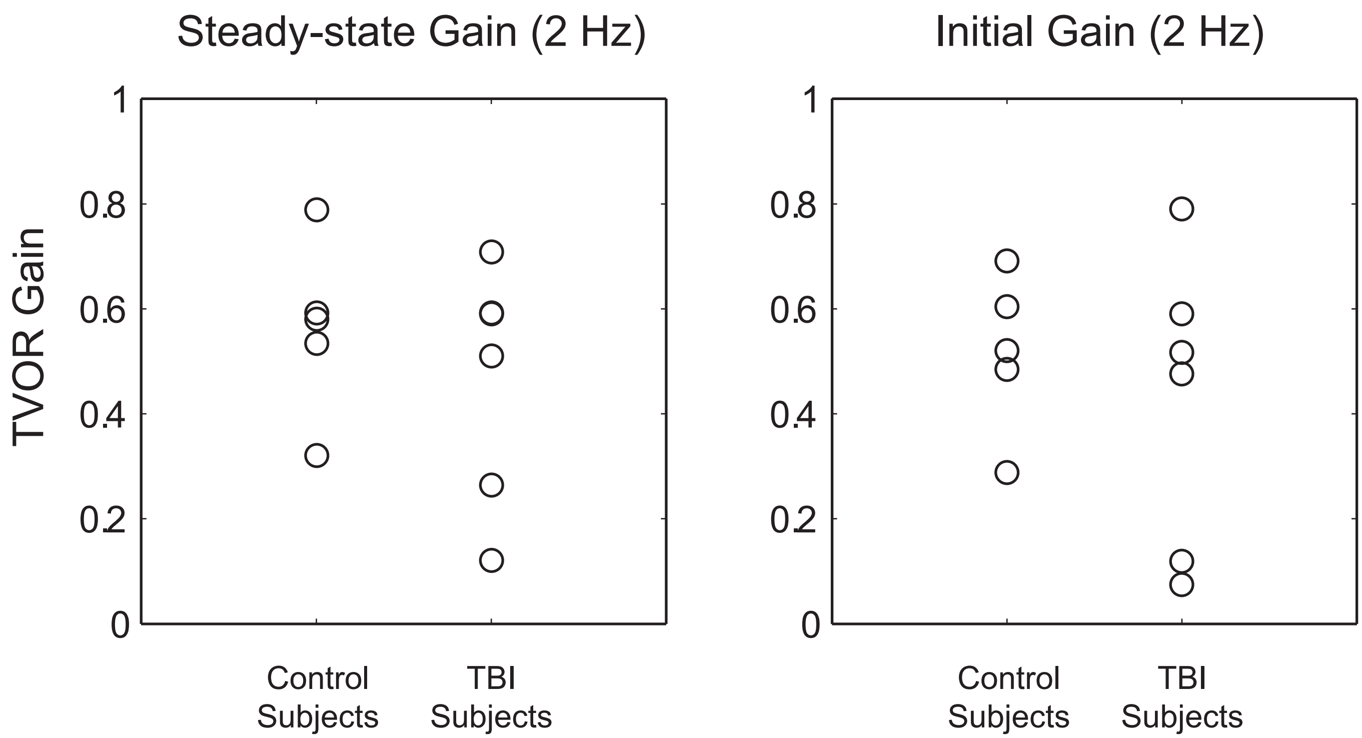

FIGURE 1: TVOR gains in control and TBI subjects for 2 Hz translations. Eye and head movement data are fit to a 2 Hz sine and gains are calculated as the ratio of measured to ideal eye velocity. The left panel shows the steady-state gain based on the sinusoidal fits, and the right panel shows the initial gain, based on the first half-cycle of motion

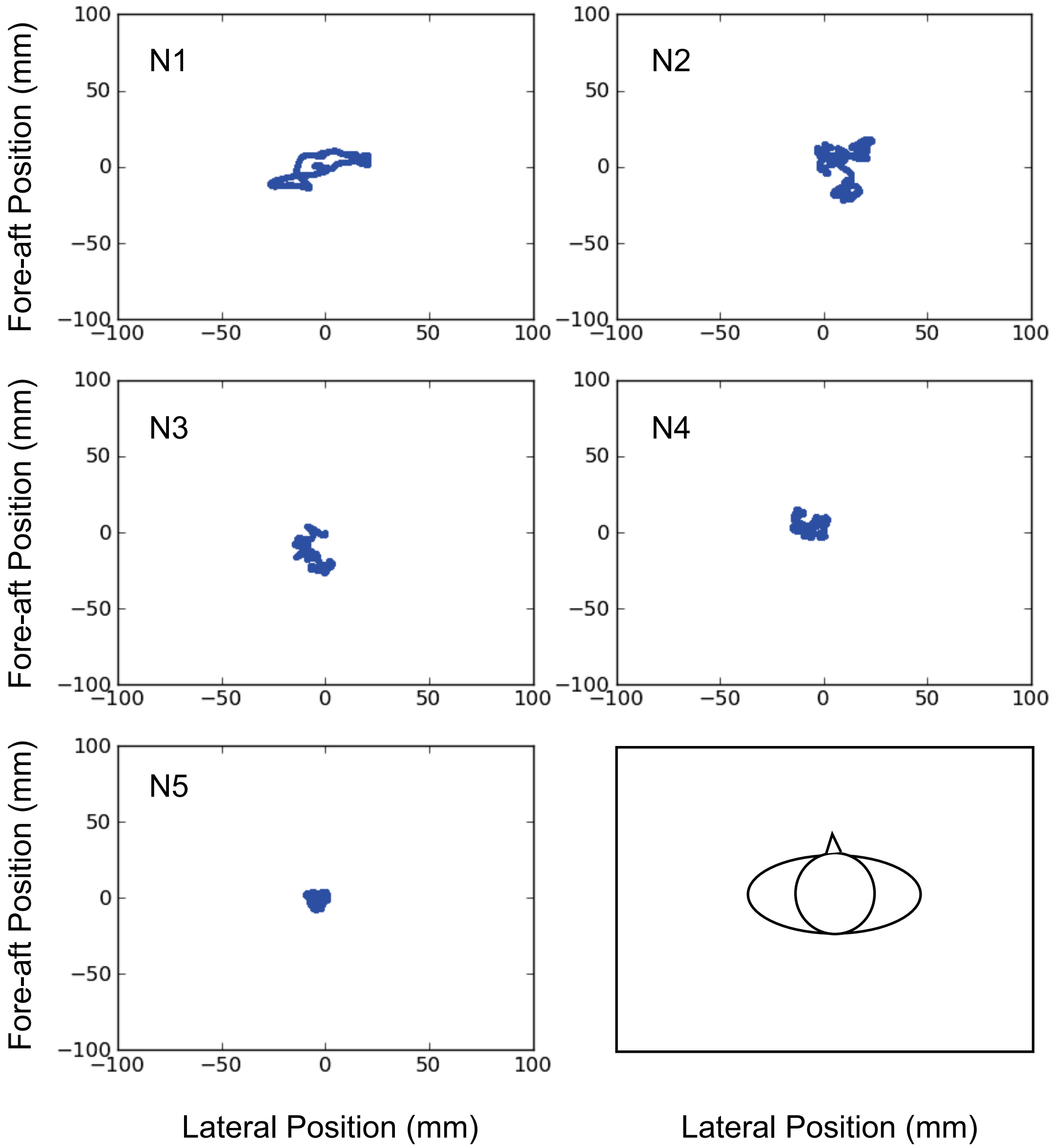

FIGURE 2: Two-dimensional plots of body sway while standing on foam with eyes open (normal subjects). Each plot represents the data from one subject, plotting fore-aft position against lateral position (sacral marker) for approximately 18 seconds after eye closure.

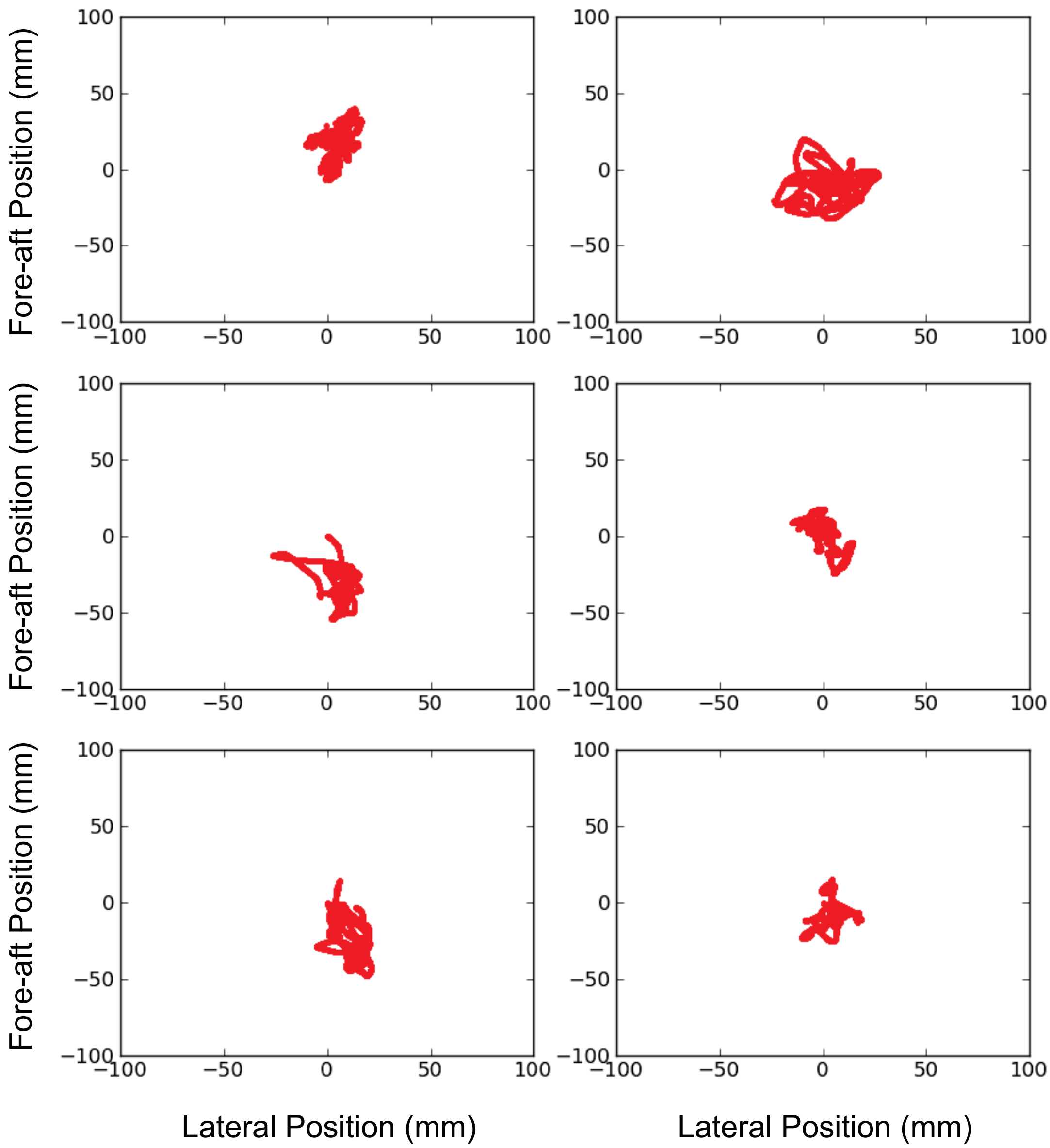

FIGURE 3: Two-dimensional plots of body sway while standing on foam with eyes open (TBI subjects). Each plot represents the data from one subject, plotting fore-aft position against lateral position (sacral marker) for approximately 18 seconds after eye closure.

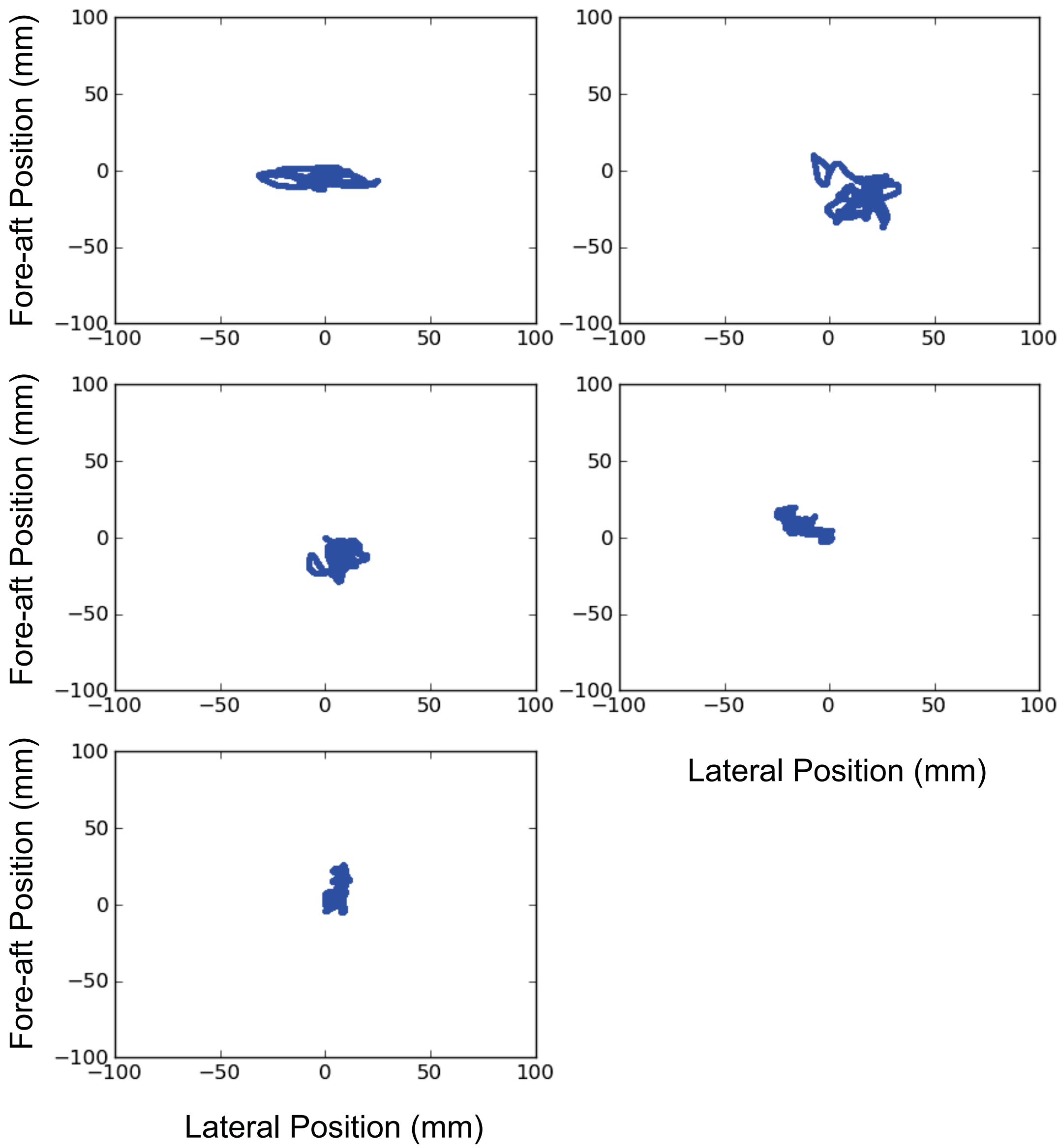

FIGURE 4: Two-dimensional plots of body sway while standing on foam with eyes closed (normal subjects). Same format as for Figure 2.

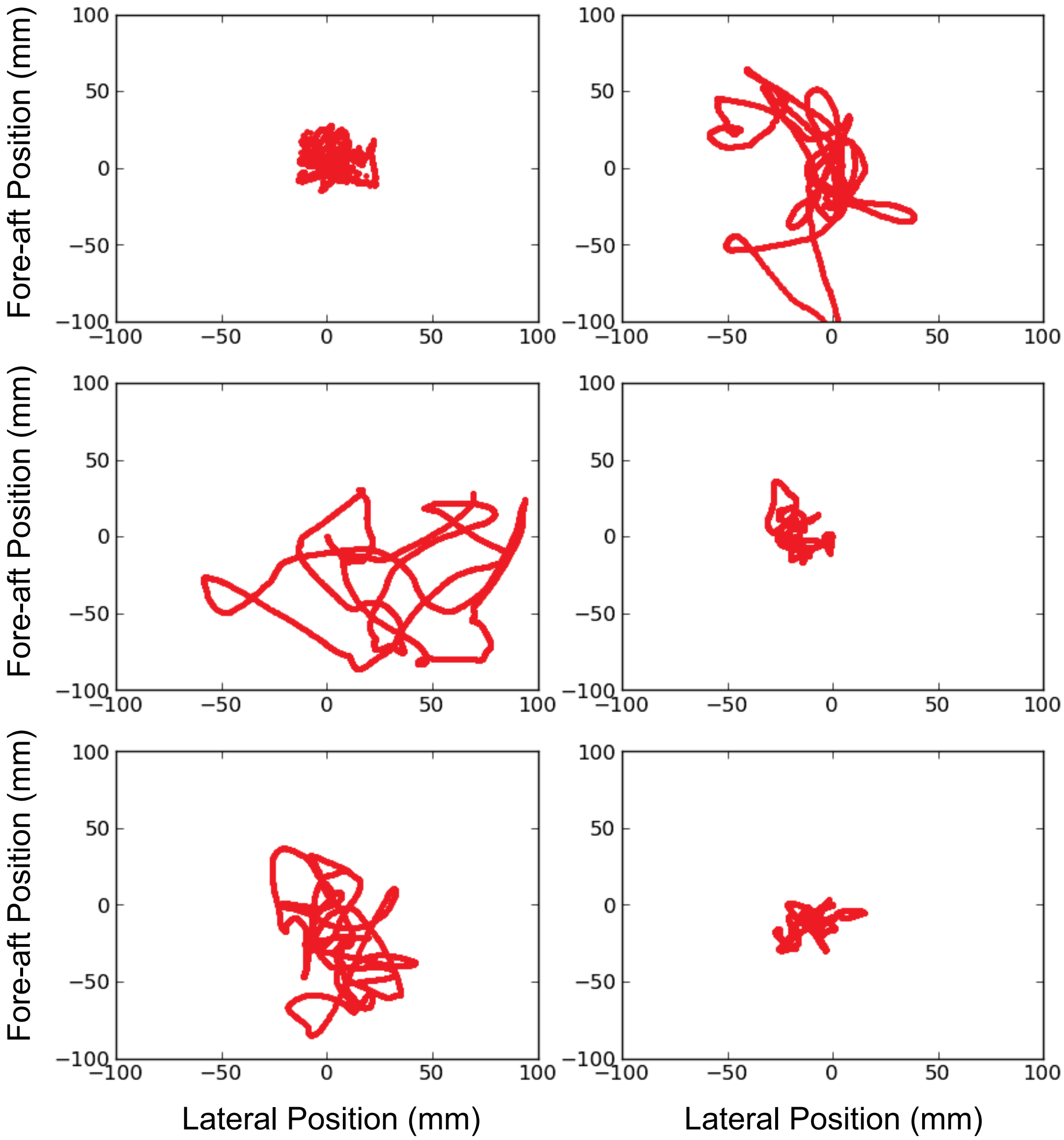

FIGURE 5: Two-dimensional plots of body sway while standing on foam with eyes closed (TBI subjects). Same formate as Figure 3. Note the greater amount of sway with eyes closed.

TAO PAN

PROFESSIONAL EXPERIENCE

Summary: Over 17 years experience (including 7 years industrial experience) in design, modeling, fabrication, and testing of microelectromechanical systems (MEMS), as well as experience in IC fabrication technology, analog/digital circuit design, analytical and numerical modeling, and design of integrated circuit and microsystem technology devices. Technical design lead on many projects, and served as Principal Investigator in SBIR (Small Business Innovation Research) grant. Device experience includes both surface (polysilicon and SOI) and bulk (KOH and Deep RIE) micromachined sensors and actuators for sensing applications in pressure, temperature sensors, flow, acoustic noise, shear stress, chemical, as well as optical switches, and inertial sensors (accelerometer and angular rate sensor). Extensive experience in industrial standard software applications such as ANSYS, OrCAD, Matlab. Extensive experience in electronic instrumentation and maintenance.

Principal Research Engineer — *Dept. of Biomedical Engineering, Learner Research Institute, Cleveland Clinic, Cleveland, OH* — *2003-2010*

- Design, modeling, and testing of MEMS devices for medical applications including ultrasonic transducers, pressure sensors, micro inductors, cell separation systems.
- ANSYS simulation of implanted capacitive pressure sensors for spinal cord recovery detection.
- Using OrCAD for transducer interface circuit simulation, verification, and optimization.
- Using industrial standard design tool (SONNET) to simulate performance of micromachined coil inductance for spinal cord recovery detection.
- Debugging and writing Matlab scripts for intravascular ultrasound data processing and imaging.
- Providing system administration for the computational facilities within the BioMEMS group.

Design Engineer — *Advanced MicroMachines., Cleveland, OH* — *1996-2002*

- Design, modeling, and testing of MEMS devices, with experience in pressure sensors, temperature sensors, flow sensors, acoustic sensors, inertial sensors (accelerometer and angular rate sensor), optical switch, and chemical sensors.
- Principal Investigator (technical and administrative) for development of angular rate sensors for aerospace applications. Designed an integrated Bi-CMOS/MEMS device that was fabricated in the inaugural run at Analog Devices.

- Key technical and MEMS device lead for chemical sensors and acoustic sensors for cross-divisional internally funded aerospace programs.
- Key technical and MEMS device lead for an integrated pressure, temperature, and flow sensor for a soft drink dispense system.
- Significant experience interfacing with production cleanroom fabrication team with additional 5-year fabrication experience for prototype devices. Utilized process modeling tools such as Suprem.
- Extensive FEA experiences with ANSYS for MEMS device modeling in support of design and fabrication efforts through the Advanced MicroMachines Business unit.
- ASIC interface circuit design for MEMS sensors through MOSIS. Experienced with circuit simulation packages like Spice.

Research Assistant	*Electrical Engineering and Applied Physics,* *Case Western Reserve University, Cleveland, OH*	*1991-1995*

- Developed microfabricated shear stress sensors with integrated signal conditioning circuitry using polysilicon surface-micromachining technology.
- Trained lab users on use of Eaton photolithography 5X stepper in IC Class 100 Microfabrication cleanroom.
- Conducted modeling of pressure sensor performance.
- Provided system administration for the computational facilities of the research group.

Research Assistant	*Institute of Microelectronics,* *Peking University; Peking, P. R. China*	*1988-1991*

Developed a timing simulator for digital NMOS integrated circuits, which converges faster than SPICE and gives better results than a logic simulator.

EDUCATION

Ph.D.	*Electrical Engineering and Applied Physics,* *Case Western Reserve University; Cleveland, OH*	*January, 1996*
Master of Science	*Computer Science and Technology,* *Peking University; Peking, P. R. China*	*July, 1991*
Bachelor of Science	*Computer Science and Technology,* *Peking University; Peking, P. R. China*	*July, 1988*

COMPUTER SKILLS

- Knowledgeable in system administration with Windows and Unix systems.
- Proficient in industrial standard software packages, such as ANSYS for finite element analysis, OrCAD for circuit design, L-Edit for ASIC and MEMS device layout, Matlab fior data processing.
- Proficient in special purpose applications, such as Photoshop for imaging editing and Premiere Pro for video editing.
- Proficient in programming with C, Fortran, Pascal,
- Proficient in general-purpose software applications such as Microsoft Office, Adobe Acrobat, etc.

AWARDS AND HONORS

››› **Best Paper Award**, *The 16th International Congress on Instrumentation in Aerospace Simulation Facilities,* July 1995, Dayton, Ohio.

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